VISION ACADEMY

people | research | education

Discussion and debate:

Use of topical antibiotics with intravitreal injections

Professor Anat Loewenstein

Dr. Paisan Ruamviboonsuk

The Vision Academy is sponsored by Bayer. This presentation has been developed independently by Vision Academy members and does not necessarily reflect the views of Bayer. This presentation reflects the views of a majority of Vision Academy members; individual views may vary. The Vision Academy Steering Committee comprises Bora Eldem, Alex Hunyor, Antonia M. Joussen, Adrian Koh, Jean-François Korobelnik, Paolo Lanzetta, Anat Loewenstein, Monica Lövestam-Adrian, Rafael Navarro, Lihteh Wu, Annabelle A. Okada, Ian Pearce, Francisco J. Rodríguez, Sebastian Wolf and David Wong.

Session aims

- To debate and discuss evidence ‘for’ and ‘against’ the use of topical antibiotics with IVT injections
- To provide a summary of the Vision Academy’s Viewpoint on the use of topical antibiotics with intravitreal injections
  - The Viewpoint can be found in your symposium pack

IVT, intravitreal

VISION ACADEMY
people | research | education

Debate:

Is there a case FOR topical antibiotics with intravitreal injections?

Professor Anat Loewenstein

Tel Aviv Sourasky Medical Center, Israel

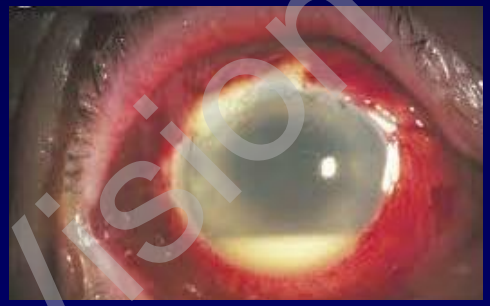
Financial and other disclosures

I have the following financial interests or relationships to disclose	Disclosure code
Allergan, Bayer, ForSight Labs, Notal Vision, Novartis	C

C, consultant

Risk of endophthalmitis with IVT injections

- **Endophthalmitis is an uncommon, potentially devastating complication of IVT injection[1]**
  - **Occurrence of endophthalmitis ranges from 1 in 1000 to 1 in 5000 injections[2]**
  - **Despite appropriate and prompt therapy, visual outcomes are often poor[3]**
- **Risk reduction strategies for the prevention of endophthalmitis are particularly important for improving overall patient outcomes[3]**

IVT, intravitreal.

1. Sachdeva MM *et al. J Ophthalmic Inflamm Infect* 2016; 6 (1): 2. 2. Sigford DK *et al. Clin Ophthalmol* 2015; 9: 773–781. 3. Schwartz SG *et al. Curr Pharm Des* 2015; 21 (32): 4703–4706.

VISION ACADEMY
people | research | education

Endophthalmitis After Intravitreal Injections: Incidence, Presentation, Management, and Visual Outcome	Dossarps D *et al. AJO* 2015; 160 (1): 17–25
Endophthalmitis After Anti-VEGF Injections	Klein KS *et al. Ophthalmology* 2009; 116 (6): 1225–1226
Incidence and clinical features of post-injection endophthalmitis according to diagnosis	Rayess N. *BJO* 2016; 100: 1058–1061
LOW ENDOPHTHALMITIS RATES AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTIONS IN AN OPERATION ROOM **A Retrospective Multicenter Study**	Freiberg FJ *et al. Retina* 2017; 0: 1–6
Post-intravitreal anti-VEGF endophthalmitis in the United Kingdom: incidence, features, risk factors and outcome	Lyall D. *Eye* 2012; 26: 1517–1526

VEGF, vascular endothelial growth factor.

Precautions for endophthalmitis prevention

General consensus on:

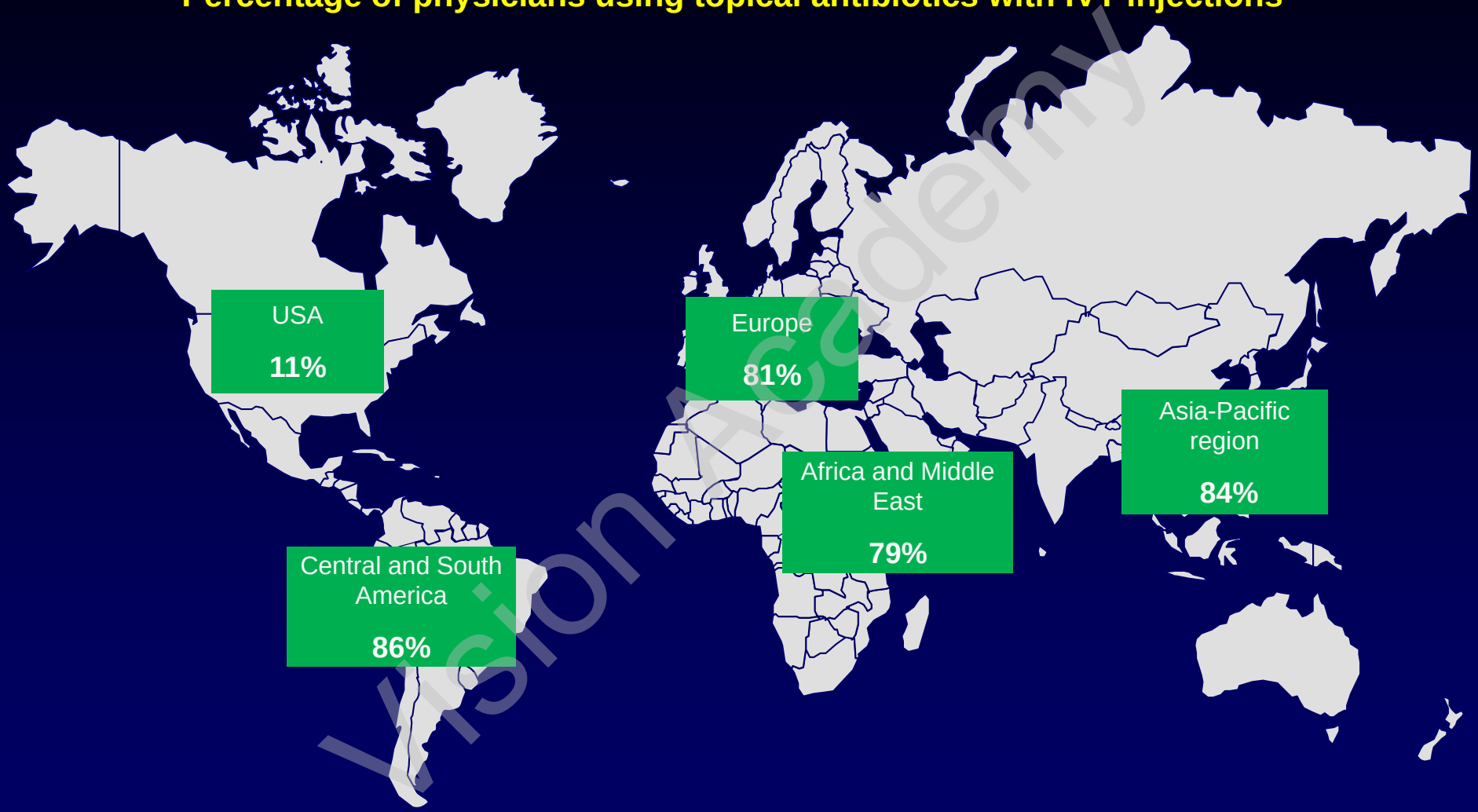
- Meticulous preparation
  - Avoidance of needle contact with eyelashes
  - Eyelid speculum
  - Drapes
- Careful attention paid to aseptic technique
- Povidone-iodine use
  - On ocular surface, in conjunctival cul-de-sac

Lack of consensus on:

- Use of sterile gloves
- Movement of conjunctiva over injection site
- **Use of pre- or post-injection antibiotics**

2014 ASRS PAT survey:

Percentage of physicians using topical antibiotics with IVT injections*



*Total percentage of physicians who prescribe topical antibiotics only in selected patients, or at any stage of the intravitreal injection process.
ASRS, American Society of Retina Specialists; IVT, intravitreal; PAT, Preferences and Trends.

Rezaei KA *et al.* 2014 Global Trends in Retina Survey. American Society of Retina Specialists; Chicago, IL, USA.

VISION ACADEMY
people | research | education

2015 ASRS PAT survey:

Percentage of physicians using topical antibiotics with IVT injections*

*Total percentage of physicians who prescribe topical antibiotics only in selected patients, or at any stage of the intravitreal injection process.
ASRS, American Society of Retina Specialists; IVT, intravitreal; PAT, Preferences and Trends.

Stone TW *et al.* 2015 Preferences and Trends Membership Survey. American Society of Retina Specialists; Chicago, IL, USA.

VISION ACADEMY
people | research | education

Regional considerations

Possible reasons for regional variations

- Perceived as the standard of care in some regions
- Personal preference
- Medico-legal considerations
- Mandated by label in some regions (e.g., Japan)
- Resources and conditions vary between countries

Regional considerations

Possible reasons for regional variations

- Perceived as the standard of care in some regions
- Personal preference
- Medico-legal considerations
- Mandated by label in some regions (e.g., Japan)
- **Resources and conditions vary between countries**

IVT injection technique and monitoring:
Updated guidelines from an expert panel

- The dramatic increase in the number of IVT injections has been accompanied by a comparable increase in evidence surrounding IVT practice patterns and techniques
- An expert panel of ophthalmologists performed a review of the literature regarding IVT injections and concluded that:

IVT, intravitreal.

Avery RL *et al. Retina* 2014; 34: S1–S18.

IVT injection technique and monitoring:
Updated guidelines from an expert panel

- The dramatic increase in the number of IVT injections has been accompanied by a comparable increase in evidence surrounding IVT practice patterns and techniques
- An expert panel of ophthalmologists performed a review of the literature regarding IVT injections and concluded that:
  - There was a **lack of evidence** to support the routine use of pre-, peri-, and post-injection antibiotics to reduce the risk of endophthalmitis
  - There was a **lack of evidence** to support the role of aerosolized droplets containing oral contaminants from the patient and/or providers as a potential source of infection
- The panel emphasized the continued importance of applying povidone-iodine and avoiding eyelid contact with the intended injection site and needle

IVT, intravitreal.

Avery RL *et al. Retina* 2014; 34: S1–S18.

IVT injection technique and monitoring:
Updated guidelines from an expert panel

- The dramatic increase in the number of IVT injections has been accompanied by a comparable increase in evidence surrounding IVT pr
- An ex of the literat
  - Th re-, peri-, an almitis
  - The zed dro or providers as a potential source of infection
- The panel emphasized the continued importance of applying povidone-iodine and avoiding eyelid contact with the intended injection site and needle

Antibiotic Use

There is insufficient evidence to support the routine use of pre-, peri- or postinjection on antibiotics to reduce the rate of endophthalmitis.

They are not against antibiotics!

IVT, intravitreal.
Avery RL *et al. Retina* 2014; 34: S1–S18.

Is there a case for using topical antibiotics with IVT injections?

Study	Injections	Retinal diseases treated	Endophthalmitis rate with topical antibiotics	Endophthalmitis rate without topical antibiotics	Statistical significance
Bhatt *et al.* 2011	4767	Multiple	0.22%	0.20%	Not significant
Bhavsar *et al.* 2012	8027	DME and PDR	0.13%	0.03%	Not significant
Bhavsar *et al.* 2015	18,839	Multiple	0.005%	Not applicable	Not applicable
Cheung *et al.* 2012	15,895	Multiple	0.061–0.084%	0.038%	Not significant
Falavarjani *et al.* 2013	5901	Multiple	0.10%	0%	Not significant
Falavarjani *et al.* 2015	8037	Multiple	0.01%	0%	Not significant
Meredith *et al.* 2015	18,509	Neovascular AMD	0.04–0.08%	0.15%	Not significant
Park *et al.* 2013	17,332	Multiple	0%	0.035%	Not significant
Porteous *et al.* 2014	6957	Not specified	Not applicable	0.04%	Not significant
Ramel *et al.* 2014	11,450	Not specified	0.03%	0.23%	p=0.024
Storey *et al.* 2014	117,171	Multiple	0.049%	0.032%	Not significant

AMD, age-related macular degeneration; DME, diabetic macular edema; IVT, intravitreal; PDR, proliferative diabetic retinopathy.

Schwartz SG *et al. Curr Pharm Des* 2015; 21 (32): 4703–4706.

VISION ACADEMY
people | research | education

Summary

- A meta-analysis and consensus paper did not find any harm in prescribing antibiotics, and in some analyses, a **lower** risk for endophthalmitis was demonstrated
- On a large-scale basis, and in various societies with diverse sanitary conditions, the need for antibiotics may vary and **should still be considered**

Debate:

Topical antibiotics SHOULD NOT be used alongside intravitreal injections

Dr. Paisan Ruamviboonsuk

Rajavithi Hospital, Thailand

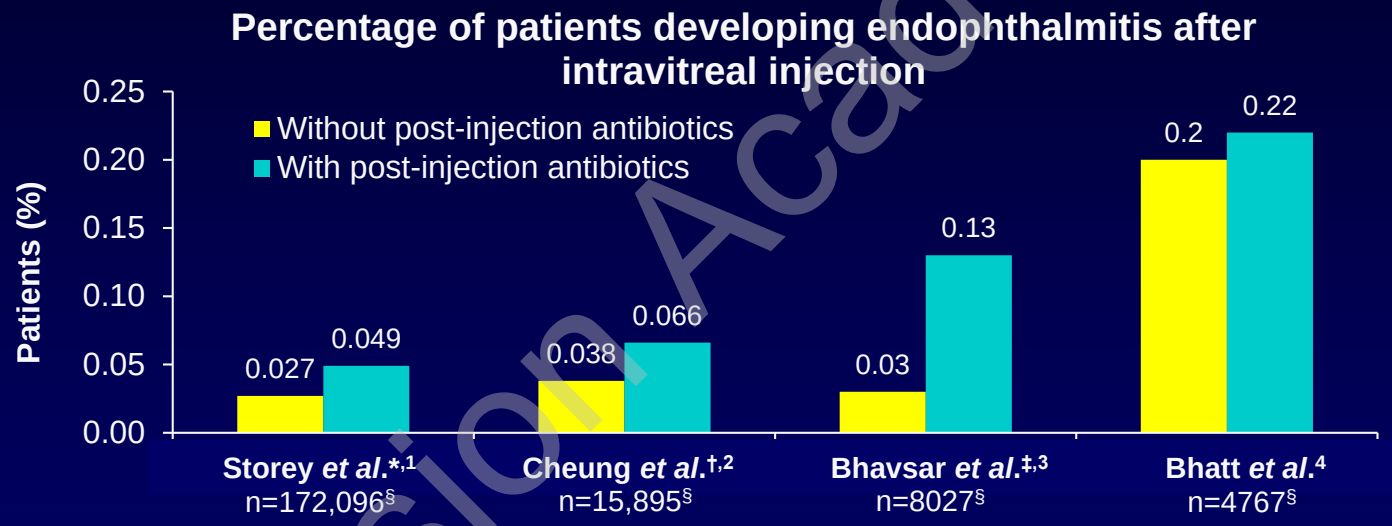
Financial and other disclosures

I have the following financial interests or relationships to disclose	Disclosure code
Novartis, Bayer, Allergan	C
Novartis, Bayer	S

C, consultant; S, grant support.

Post-injection antibiotics have no effect on the rate of endophthalmitis

- **Large studies have shown that the use of post-injection antibiotics does not reduce the incidence of endophthalmitis[1–4]**



- **A similar outcome was also reported in one of the largest (316,576 injections) retrospective, nationwide studies conducted in France[5]**

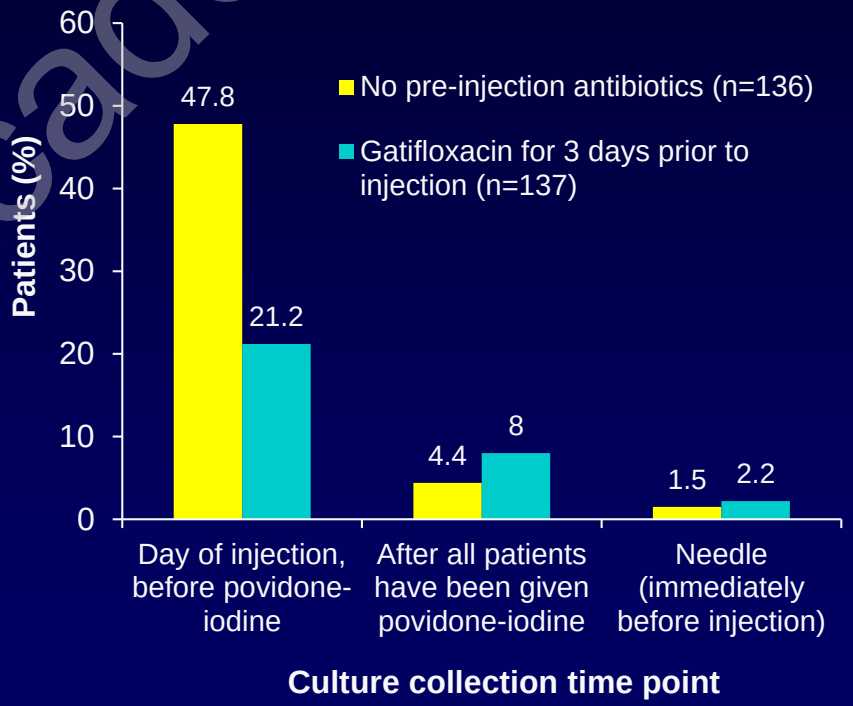
*For the Post-Injection Endophthalmitis Study Team. †8259 patients were given antibiotics for 5 days after injection; 2370 patients received antibiotics immediately after injection. ‡For the Diabetic Retinopathy Clinical Research Network. §Injections.

1. Storey P *et al. Graefes Arch Clin Exp Ophthalmol* 2016; 254 (2): 235–242. 2. Cheung CS *et al. Ophthalmology* 2012; 119 (8): 1609–1614.
3. Bhavsar AR *et al. Arch Ophthalmol* 2012; 130 (6): 809–810. 4. Bhatt SS *et al. Retina* 2011; 31 (10): 2032–2036.
5. Dossarps D *et al. Am J Ophthalmol* 2015; 160 (1): 17–25.e1.

Pre-injection antibiotics are not associated with lower bacterial loads at the injection site*

- The use of topical antibiotics (combined with povidone-iodine) before cataract surgery has been shown to result in reduced bacterial colony counts[1]
- This benefit does not appear to translate to the use of topical antibiotics administered before an IVT injection
- There is no additional benefit of pre-injection antibiotic use when combined with povidone-iodine
  - Povidone-iodine reduces the number of bacterial colonies by 91%[3]
  - Povidone-iodine lowers the risk of endophthalmitis to 0.06% (vs. 0.24%)[4]

Percentage of patients with conjunctival culture positivity with and without pre-injection antibiotics[2]



*When given in addition to povidone-iodine.
IVT, intravitreal.

1. Isenberg SJ *et al. Arch Ophthalmol* 1985; 103 (9): 1340–1342. 2. Moss JM *et al. Ophthalmology* 2009; 116 (8): 1498–1501. 3. Apt L *et al. Arch Ophthalmol* 1984; 102 (5): 728–729. 4. Speaker MG *et al. Ophthalmology* 1991; 98 (12): 1769–1775.

VISION ACADEMY
people | research | education

Pooled incidence of endophthalmitis

Review

POOLED ESTIMATES OF INCIDENCE OF ENDOPHTHALMITIS AFTER INTRAVITREAL INJECTION OF ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS WITH AND WITHOUT TOPICAL ANTIBIOTIC PROPHYLAXIS

MICHELE REIBALDI, MD, PHD,* ALFREDO PULVIRENTI, PHD,† TERESIO AVITABILE, MD,* VINCENZA BONFIGLIO, MD, PHD,* ANDREA RUSSO, MD, PHD,* CESARE MARIOTTI, MD,‡ CLAUDIO BUCOLO, PHD,§ RODOLFO MASTROPASQUA, MD,¶ GUGLIELMO PARISI, MD,* ANTONIO LONGO, MD, PHD*

Purpose: To assess the effect of topical antibiotic prophylaxis on postoperative endophthalmitis after intravitreal injection of anti–vascular endothelial growth factor agents.

Methods: A systematic literature search was performed from inception to March 2016 using PubMed, Medline, Web of Science, Embase, and the Cochrane Library, to identify articles that reported cases of endophthalmitis after intravitreal injection of anti–vascular endothelial growth factor agents. We used a pooled analysis to estimate the incidence of cases of endophthalmitis who developed after injections performed with and without topical antibiotic prophylaxis. We used regression analysis to explore the effects of study characteristics on heterogeneity.

Results: From our search of electronic databases, we identified and screened 4,561 unique records. We judged 60 articles to have reported findings for cohorts of patients who met our inclusion criteria, (12 arms of randomized clinical trials, 11 prospective cohort studies, and 37 retrospective cohort studies), which included 244 cases of endophthalmitis and 639,391 intravitreal injections of anti–vascular endothelial growth factor agents. The final pooled estimate endophthalmitis proportions were 9/10,000 (95% confidence interval,

Reibaldi M *et al. Retina* 2018; 38 (1): 1–11.

Pooled incidence of endophthalmitis

- The review paper by Reibaldi *et al.* identified and screened 4561 records; 60 articles met the inclusion criteria (12 arms of RCTs, 11 prospective cohorts, and 37 retrospective cohorts) and included 244 cases of endophthalmitis and 639,391 IVT injections of anti-VEGF
- The final pooled estimate of endophthalmitis proportions were:
  - 9 / 10,000 (95% CI, 7 / 10,000–12 / 10,000) in the antibiotic-treated group
  - 3 / 10,000 (95% CI, 2 / 10,000–5 / 10,000) in the untreated group

CI, confidence interval; IVT, intravitreal; RCTs, randomized controlled trials; VEGF, vascular endothelial growth factor.

Reibaldi M *et al. Retina* 2018; 38 (1): 1–11.

Use of antibiotics can interfere with models of care

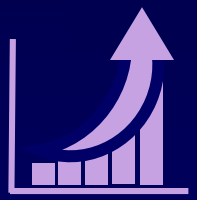
- **For patients on a PRN regimen with monthly monitoring, a requirement for pre-injection antibiotics would mean that IVT injections could not take place during the monitoring visit[1]**
  - **Increased burden of appointments for patients and clinics**
- **Post-injection antibiotics have been estimated to increase the financial burden on the US healthcare system by an additional $64 million per year[2]**

Burden on the patient

Additional clinic visits may affect adherence to treatment

Burden on clinic capacity

Increased clinic visits require resources and clinician time



Burden on the healthcare system

Increased costs of delivering IVT therapy

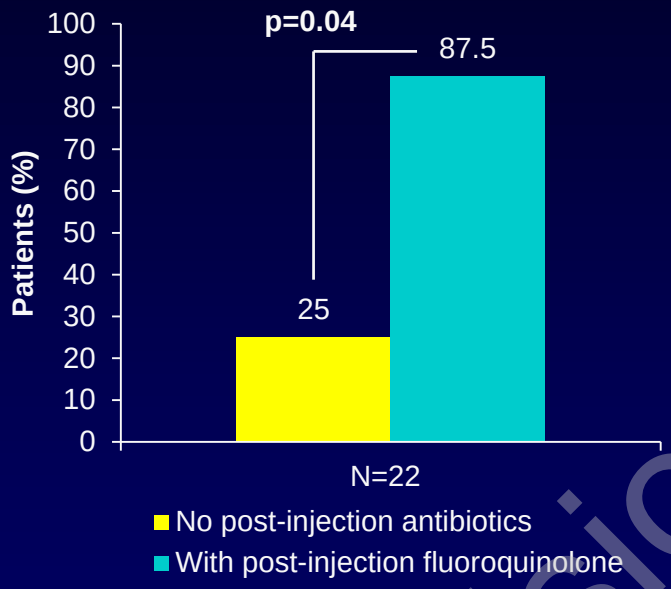
IVT, intravitreal; PRN, *pro re nata* (as needed).

1. Hunyor AP *et al. Acta Ophthalmol* 2016; Epub ahead of print (DOI: 10.1111/aos.13417). 2. Chen RW *et al. JAMA Ophthalmol* 2013; 131 (7): 840–842.

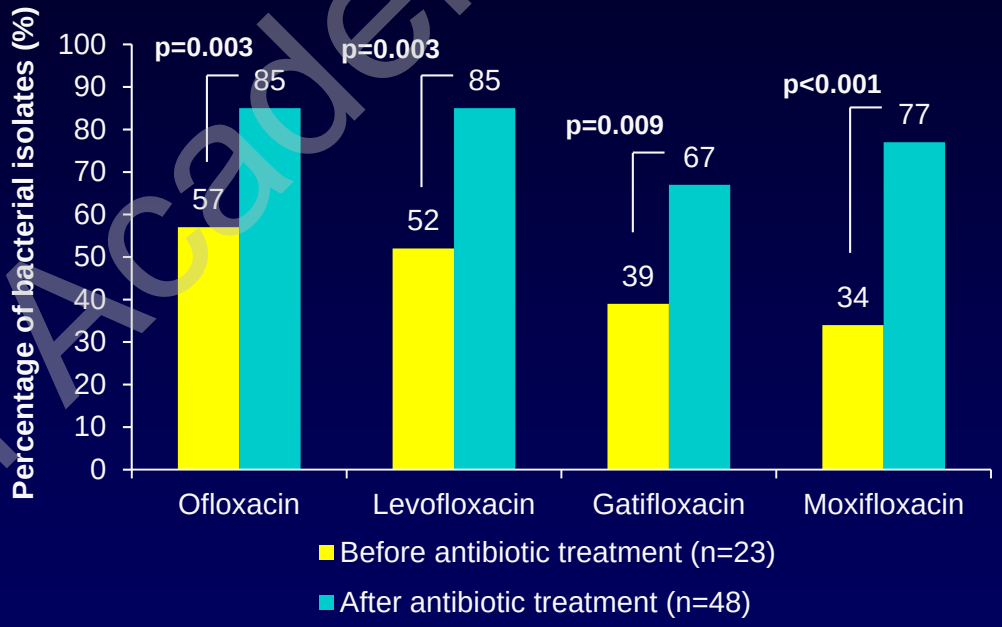
VISION ACADEMY
people | research | education

Use of topical antibiotics increases antibiotic resistance

Percentage of patients with ocular colonies resistant to fluoroquinolones[1]



Percentage of conjunctival bacterial isolates resistant to fluoroquinolones, before and after 3 intraocular injections with post-injection antibiotics[2]



Use of povidone-iodine alone with IVT injections **does not** lead to bacterial resistance[3]

IVT, intravitreal.

1. Milder E *et al. Ophthalmology* 2012; 119 (7): 1420–1424. 2. Kim SJ *et al. Ophthalmology* 2011; 118 (7): 1358–1363.
3. Hsu J *et al. Am J Ophthalmol* 2014; 157 (3): 514–518.e1.

VISION ACADEMY
people | research | education

Lack of antibiotic penetration into the vitreous

- **A prospective randomized study demonstrated that topical antibiotic administration leads to effective levels in the aqueous but not in the vitreous**
  - **The concentrations in the vitreous did not exceed the MIC_{90} for the most common bacterial pathogens causing acute postoperative endophthalmitis**

	Mean vitreous concentration ± SD (µg/mL)		MIC_{90} (µg/mL)		
Topical antibiotic	**3-day pre-surgery regimen* (n=3)**	**1-hour pre-surgery regimen† (n=3)**	***Staphylococcus aureus***	***Staphylococcus epidermidis***	***Staphylococcus pneumoniae***
Moxifloxacin 0.5%	0.011 ± 0.008	0.012 ± 0.011	0.064	0.047	0.125
Gatifloxacin 0.3%	0.008 ± 0.006	0.001 ± 0.0003	0.11	0.09	0.22

*Four doses per day for 3 days prior to surgery (patient-administered; 100% patient compliance); †One drop every 15 minutes for a total of three doses administered 1 hour prior to surgery.
MIC_{90}, minimum inhibitory concentration for 90% of isolates; SD, standard deviation.
Costello P *et al. Retina* 2006; 26 (2): 191–195.

VISION ACADEMY

people | research | education

What is the Vision Academy's position?

Vision Academy Viewpoint:

Use of topical antibiotics with intravitreal injections

Based on an extensive literature search, the Vision Academy **does not** recommend the use of topical antibiotics alongside IVT injections

There is **no evidence** for the prevention of infection[1]

There is **no evidence** for a reduction in infection-related morbidity[2]

Repeated use of antibiotics is proven to **increase** the occurrence of **antibiotic resistance** and can potentially increase virulence[1]

There is an **additional and unnecessary cost and burden** to patients, physicians, and healthcare systems[1]

IVT, intravitreal.

1. Merani R *et al. Int J Retina Vitreous* 2015; 1: 9. 2. Hunyor AP *et al. Acta Ophthalmol* 2017; Epub ahead of print (DOI: 10.1111/aos.13417)

VISION ACADEMY
people | research | education

Vision Academy Viewpoint:

Use of topical antibiotics with intravitreal injections

Topical antibiotic use **prior to** IVT injection

- Most infections result from inoculation of organisms at the time of injection
- No prospective studies demonstrating that pre-injection antibiotics reduce the risk of endophthalmitis[1]

Topical antibiotic use **concurrent with** or **after** IVT injection

- No additional benefit of post-injection antibiotics in preventing endophthalmitis[2,3]

General consensus

Variation in opinion

IVT, intravitreal.

1. Merani R *et al*. *Int J Retina Vitreous* 2015; 1: 9. 2. Li AL *et al. Retina* 2016; 36 (7): 1349–1356.
3. Storey P *et al. Ophthalmology* 2014; 121 (1): 283–289.

VISION ACADEMY
people | research | education

Vision Academy Viewpoint:

Use of topical antibiotics with intravitreal injections

Antibiotic resistance

- Several studies have demonstrated increasing resistance of conjunctival flora to topical antibiotics[1,2]
- Resistance to fluoroquinolones, the most commonly used topical antibiotics in many regions, may have serious ramifications in other procedures (e.g., cataract surgery)

Antibiotic penetration

- Topical administration leads to effective antibiotic levels in the aqueous but not in the vitreous[3]

General consensus

Variation in opinion

1. Merani R *et al*. *Int J Retina Vitreous* 2015; 1: 9. 2. Milder *et al. Ophthalmology* 2012; 119: 1420–1424. 3. Costello P *et al. Retina* 2006; 26 (2): 191–195.

VISION ACADEMY
people | research | education

Vision Academy Viewpoint:

Use of topical antibiotics with intravitreal injections

Significant regional differences

- Reasons for continued use of topical antibiotics with IVT injections include:
  - Personal preference
  - Peer pressure
  - Medico-legal concerns

Challenge in changing clinical practice

- Changes in practice habits may be achieved through the revision of drug labels and the amendment of local and professional society guidelines

General consensus

Variation in opinion

IVT, intravitreal.

VISION ACADEMY
people | research | education

Summary

The Vision Academy **does not recommend the use of topical antibiotics** alongside IVT injections

There is a **lack of evidence** supporting any benefit for topical antibiotic prophylaxis against post-injection endophthalmitis

There is a growing body of evidence detailing **increased antibiotic resistance** in patients receiving topical antibiotics

Product information for IVT medications should be updated to reflect this recommendation and to **remove barriers to clinicians wishing to change their practice**

IVT, intravitreal.